Postlicensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine

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Context In June 2006, the Food and Drug Administration licensed the quadrivalent human papillomavirus (types 6, 11, 16, and 18) recombinant vaccine (qHPV) in the United States for use in females aged 9 to 26 years; the Advisory Committee on Immunization Practices then recommended qHPV for routine vaccination of girls aged 11 to 12 years.

Objective To summarize reports to the Vaccine Adverse Event Reporting System (VAERS) following receipt of qHPV.

Design, Setting, and Participants Review and describe adverse events following immunization (AEFIs) reported to VAERS, a national, voluntary, passive surveillance system, from June 1, 2006, through December 31, 2008. Additional analyses were performed for some AEFIs in prelicensure trials, those of unusual severity, or those that had received public attention. Statistical data mining, including proportional reporting ratios (PRRs) and empirical Bayesian geometric mean methods, were used to detect disproportionality in reporting.

Main Outcome Measures Numbers of reported AEFIs, reporting rates (reports per 100 000 doses of distributed vaccine or per person-years at risk), and comparisons with expected background rates.

Results VAERS received 12 424 reports of AEFIs following qHPV distribution, a rate of 53.9 reports per 100 000 doses distributed. A total of 772 reports (6.2% of all reports) described serious AEFIs, including 32 reports of death. The reporting rates per 100 000 qHPV doses distributed were 8.2 for syncope; 7.5 for local site reactions; 6.8 for dizziness; 5.0 for nausea; 4.1 for headache; 3.1 for hypersensitivity reactions; 2.6 for urticaria; 0.2 for venous thromboembolic events, autoimmune disorders, and Guillain-Barré syndrome; 0.1 for anaphylaxis and death; 0.04 for transverse myelitis and pancreatitis; and 0.009 for motor neuron disease. Disproportional reporting of syncope and venous thromboembolic events was noted with data mining methods.

Conclusions Most of the AEFI rates were not greater than the background rates compared with other vaccines, but there was disproportional reporting of syncope and venous thromboembolic events. The significance of these findings must be tempered with the limitations (possible underreporting) of a passive reporting system.

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On June 8, 2006, the Food and Drug Administration (FDA) licensed the quadrivalent human papillomavirus recombinant vaccine (qHPV) (Gardasil; Merck & Co, Inc, Whitehouse Station, New Jersey) for females aged 9 to 26 years to prevent infection with genital human papillomavirus (HPV) types 6, 11, 16, and 18.[1] Later that month, the Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination of females aged 11 to 12 years with 3 doses of qHPV and catch-up vaccination for females aged 13 to 26 years. Doses are administered intramuscularly on a schedule of 0, 2, and 6 months.[2] The viruses HPV-16 and HPV-18 can cause cervical cancer, other anogenital cancers, and precancerous or dysplastic lesions and are responsible for about 70% of cervical cancers worldwide.[3] The viruses HPV-6 and HPV-11 are the most common causes of genital warts.

See also pp 781 and 795.

Prior to licensure, clinical trials were conducted in more than 21 000 women. Vaccination with qHPV was 90% to 100% effective in preventing precancerous cervical, vaginal, and vulvar lesions and genital warts caused by infection with the relevant HPV types (6, 11, 16, or 18) in women aged 15 to 26 years who were uninfected prior to vaccination.[4,5] Additional immunogenicity and safety studies in 9- to 15-year-

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olds demonstrated high seropositivity postvaccination; geometric mean antibody titers were as high as those of women aged 16 to 23 years in the efficacy trials and, by postvaccination month 7, were 1.7- to 2.7-fold higher.[6]

In the clinical trials, the incidence of solicited systemic clinical adverse events following immunization (AEFIs) was similar in the vaccine group (59%) and the placebo group (60%). Headache was the most commonly reported systemic AEFI in both groups (qHPV, 28.2%; placebo, 28.4%). Proportions of fever (13.0% vs 11.2%) and nausea (6.7% vs 6.5%) were slightly higher in the vaccine recipients vs the placebo group. The rates of serious AEFIs were comparable between the 2 groups (<0.1%). There was a slightly higher number of severe injection site reactions in the vaccine group (n=10, 2.2%) compared with the placebo group (n=4, 0.9%) in the 5 days after vaccination.[1]

With more than 23 million qHPV doses distributed in the United States as of December 31, 2008 (number provided by manufacturer, http://www.cdc.gov/vaccinesafety/vaers/gardasil.htm), postlicensure safety monitoring can detect AEFIs too rare to have been detected during prelicensure trials. This article summarizes data from the US Vaccine Adverse Event Reporting System (VAERS) for the 2.5 years following licensure.

METHODS

We analyzed qHPV reports received by VAERS from June 1, 2006, through December 31, 2008. This voluntary, national, passive surveillance system was established in 1990 and is operated jointly by the US Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). Manufacturers, health care workers, patients or their parents, and others submit reports to VAERS.[7] Although manufacturer reporting to VAERS is required, most information comes from physicians, patients, or other primary reporters.[8] This analysis included only US reports to VAERS, which usually have more complete information and more feasible follow-up review of medical records than foreign reports. In addition, we had only US dose distribution data for calculation of reporting rates (RRs).

To code reported symptoms, VAERS uses a clinically validated, internationally standardized terminology, the Medical Dictionary for Regulatory Activities (MedDRA).[9] Each report may have several assigned MedDRA codes. We searched the VAERS database using MedDRA codes for specific AEFIs of interest and predefined groups of MedDRA codes for local reactions and hypersensitivity reactions.

We classified VAERS reports as serious according to the FDA regulatory definition (21 CFR §314.80) of a serious AEFI as one that is life threatening; results in death, permanent disability, congenital anomaly, hospitalization, or prolonged hospitalization; or necessitates medical or surgical intervention to preclude one of these outcomes.[10] We reviewed serious reports to identify primary AEs that needed further study. Onset interval is the number of days from the time of vaccination to the onset of earliest reported symptoms. The number of doses distributed in the United States (23 051 336), obtained from the vaccine manufacturer (number provided by manufacturer, http://www.cdc.gov/vaccinesafety/vaers/gardasil.htm), provided the denominator to estimate RRs.

Based on prelicensure safety data and the severity of or public attention to reported AEFIs, we performed detailed case reviews and separate analyses for syncope, dizziness, nausea, headache, local injection site reactions, hypersensitivity reactions including anaphylaxis, Guillain-Barré syndrome (GBS), transverse myelitis, pancreatitis, venous thromboembolic events (VTEs), deaths, and pregnancy outcomes.

Disproportionality screening with the empirical Bayesian geometric mean (EBGM) method, using Empirica WebVDME software (Phase Forward, Waltham, Massachusetts), identified AEFIs reported during the first year of licensure that were more frequent than expected.[11,12] We used the lower 5% bound of the 90% confidence interval for the EBGM (EB05) of 2 or higher, following criteria outlined by Szarfman et al,[13] to select AEFIs for further review. We also used proportional reporting ratio (PRR), another method to detect potential associations between reported AEFIs and a drug or vaccine, to compare the proportion of selected AEFI reports for qHPV with the proportion of selected AEFI reports for all other vaccines by age group and sex.[14,15] We applied the PRR screening criteria that Evans[15] proposed: number of cases of 3 or more, PRR of 2 or more, and χ^2 of 4 or more.

Given the association of GBS with the 1976 swine influenza vaccine and more recently with quadrivalent meningococcal conjugate vaccine,[16] there has been concern regarding the possibility of an association between GBS and other vaccines, including qHPV.[17,18] Clinical subject matter experts from the CDC Clinical Immunization Safety Assessment Network reviewed reports coded with the MedDRA term *GBS* or with text containing *GBS* or *Guillain-Barré*. Cases were classified as confirmed GBS if they met the proposed Brighton Collaboration GBS case definition.[19] Reports with insufficient information could not be classified. We used Healthcare Cost and Utilization Project data for 2000 through 2004 to estimate a background rate of GBS among 9- to 26-year-old females.[20]

The GBS reporting rate to VAERS was calculated as the number of reported GBS cases divided by the estimated person-time at risk, based on 6 weeks after each dose. This GBS reporting rate was compared with the background rate among females aged 9 to 26 years. From June 1, 2006, through December 31, 2008, there were 23 051 336 doses of qHPV distributed in the United States. Based on a 6-week window of biological plausibility after immunization, this gives a total of 2 650 667 person-years at risk.

Potential anaphylaxis reports were selected using the MedDRA terms *anaphylaxis* and *anaphylactic reaction*. Clinical subject matter experts from the CDC Clinical Immunization Safety Assessment Network reviewed reports to confirm the diagnosis of anaphylaxis. Reports were classified as anaphylaxis if they met the Brighton case definition.[21]

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Table 1. Severity of qHPV Adverse Events Following Immunization in the United States by Age, Reported to VAERS June 1, 2006, Through December 31, 2008

	Reports by AEFI Severity, No.				
Age Group, y	Death	Nonfatal Serious	Nonserious	Total, No.	Reporting Rate[a]
<9	0	0	41	41	0.2
9-10	0	11	160	171	0.7
11-12	2	60	950	1012	4.4
13-17	9	332	4009	4350	18.9
18-26	9	262	3687	3958	17.2
>26	0	16	258	274	9.9
Unknown	12	59	2547	2618	
Total	**32**	**740**	**11 652**	**12 424**	**53.9**

Abbreviations: AEFI, adverse event following immunization; qHPV, quadrivalent human papillomavirus recombinant vaccine; VAERS, Vaccine Adverse Event Reporting System.
[a] Reports per 100 000 doses distributed.

Because VAERS is a legally mandated, government-sponsored surveillance system, institutional review board approval and informed consent were not required.

RESULTS

From June 1, 2006, through December 31, 2008, VAERS received 12 424 reports of AEFIs following receipt of qHPV (TABLE 1), an overall reporting rate of 53.9 reports per 100 000 vaccine doses distributed. The majority of reports (8471/12 424, or 68%) were submitted by the manufacturer, compared with an overall rate of 40% for VAERS reports on other vaccines. During the same time period, manufacturer reports accounted for 14.5% of the meningococcal conjugate vaccine reports and 7.5% of the reports for tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine submitted to VAERS. Of the 8471 manufacturer reports for qHPV AEFIs, 7561 (89%) had insufficient identifying information to permit clinical follow-up or review. Additional sources of reporting included providers (17%), patients or parents (4%), state health clinics (1%), and "others" (11%).

In 9910 of 12 424 reports (80%), qHPV was the only vaccine identified. Patients received qHPV and quadrivalent meningococcal conjugate vaccine simultaneously in 775 of the AEFI reports (6%); the remaining 14% of reports described a variety of other vaccine combinations. Of the 8247 reports that included onset interval, 4393 (40%) occurred on the day of vaccination. Females accounted for 97% (12 039/12 424) of the patients for whom an AEFI was reported; the remaining 3% included males and reports with unspecified gender. Of 47 reports of qHPV administered to males, 25 (53%) were unintentional (medical errors with wrong vaccine administered), 17 (36%) were identified as off-label use, and 5 were from male HPV study participants. Among 9396 reports (77%) with dose information, 5772 (61%) followed the first dose, 2380 (25%) followed the second dose, and 1183 (13%) followed the third dose of qHPV. In addition, 61 (1%) inadvertently received 4 or more doses.

The most frequently reported AEFIs included syncope (n=1847, 15%), dizziness (n=1763, 14%), nausea (n=1170, 9%), headache (n=957, 8%), and injection site reactions (n=926, 7.5%). These overall aggregate numbers must be interpreted with caution since each VAERS report usually includes multiple codes; thus, there were 46 932 total codes for 12 424 reports, for an average of 3.7 codes per report (range, 2-10). Also, review of individual reports revealed coding errors and occasional duplicate coding.

Serious Reports

Among the 12 424 AEFI reports, 772 (6.2%) were serious, including 32 reports of death, 20 of which had medical records, autopsy, or death certificates available for evaluation. Sources of serious VAERS reports included manufacturer (66%), patient/parent (11%), clinician (10%), state health clinic (1%), and "other" (12%). The most frequent serious symptom/MedDRA preferred-term codes included 159 reports of headache (21%), 119 nausea (16%), 113 dizziness (15%), 102 vomiting (13%), 102 pyrexia (13%), 102 fatigue (13%), and 98 syncope (13%). Medically important serious events included 8 reports of anaphylactic reaction (1%), 9 deep vein thrombosis (1.2%), 31 GBS (4%), 25 hypersensitivity (2.5%), 10 transverse myelitis (1.3%), 6 pancreatitis (0.8%), 14 pulmonary embolism (1.8%), 23 death (3%), 68 convulsion (8.8%), 30 urticaria (3.9%), and 9 autoimmune disorder (1.2%).

Local Injection Site Reactions

There were 1741 reports with at least 1 of the MedDRA coding terms for local reactions (TABLE 2); 684 (39%) occurred on the day of vaccination. The median onset interval was 0 days after vaccination (same day as vaccination) with a range of 0 to 408 days; 1338 reports (77%) identified qHPV alone. The most common local reaction reports included injection site pain (n=926, 53%), injection site erythema (n=490, 28%), and injection site swelling (n=385, 22%). Forty-one reports (2%) involving local reactions were classified as serious. Review of these cases showed that 20 reports did not meet the FDA definition of serious; all of these were reported by the manufacturer. There were 4 cases reported as cellulitis and 1 case reported as an intra-articular injection. In the other 15 reports, local reactions were incidental and not the primary AEFIs contributing to severity.

Syncope, Dizziness, and Nausea

There were 1896 reports with the coding term *syncope* or *syncope vasovagal*, 1572 with *dizziness*, and 1164 with *nausea* (Table 2). Only 62 reports de-

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scribed all 3 events in the same individual. The qHPV was the only vaccine given in 74% of the syncope/vasovagal syncope reports, 73% of the dizziness reports, and 78% of the nausea reports. Of the reports describing syncope/vasovagal syncope, dizziness, or nausea, 94%, 90%, and 95%, respectively, were classified as nonserious. Among reports with known onset intervals, the event occurred on the same day as vaccination for 90% (1107/1228) of syncopal reports, 75% (930/1233) of dizziness reports, and 63% (610/970) of nausea reports. Of the events that occurred on the day of vaccination and where a more specific time frame was given, more than half immediately (≤15 minutes) followed vaccination. Among the 1896 syncopal reports, 293 (15%) resulted in a fall and 200 falls (68%) resulted in a head injury. Head injuries included 9 fractures (6 nose, 2 skull, and 1 maxillary), 18 dental injuries, 9 concussions, 17 contusions, 5 intracranial hemorrhages (1 subdural hematoma, 1 subarachnoid hemorrhage, 3 not otherwise specified), and 45 lacerations (38 of which required sutures). In addition, there were 7 reports of contusions on elbows or knees. The EB05 (2.28) for syncope was the only positive signal identified with EBGM methods.

Headaches

There were 937 reports of headaches after qHPV vaccination (Table 2). These accounted for 7.7% of the total AEFIs reported. One hundred fifty of these reports (16%) were coded as serious. The most common reason for being classified as a "serious" report was hospitalization for neurologic evaluation after a syncope-related fall.

Hypersensitivity Reactions

There were 725 reports with a coding term indicative of hypersensitivity (Table 2). Review of the reports showed that 31 reports were coded incorrectly. In addition, there was 1 hearsay case that could be not evaluated, leaving 693 total hypersensitivity cases. Of the 693 hypersensitivity reports, 416 (60%) were from the manufacturer, 178 (26%) were from the health care professional, 24 (3%) were from a parent or patient, and 75 (11%) were from an "other" source.

Hypersensitivity reports included 600 of urticaria (87%); 95 rash (14%); 95 pruritus (14%); 42 arthralgia (6%); 28 anaphylactic reaction (4%); 23 generalized rash (3%); 22 pruritic rash (3%); and rare reports (<1%) of angioedema, dermatographism, serum sickness, bronchospasm, and eye swelling. Five hundred fifty-six reports (80%) were attributed to qHPV alone.

The time interval between vaccination and onset of symptoms could not be calculated for 150 reports. For the reports where time interval was available, more than half of the cases were reported on the same day as (n=246, 35%) or the next day after (n=126, 18%) vaccination. The median onset interval was 1 day with a range of 0 to 271 days. No dose information was provided in 106 reports; 82 of these (77%) were manufacturer reports. Most hypersensitivity reports (n=393, 78%) occurred after dose 1, 160 (23%) occurred after dose 2, and 53 (8%) occurred after dose 3. The overall RR was 3.1 of 100 000 doses distributed.

There were 600 reports of urticaria to VAERS, including 178 reports (30%) of generalized urticaria, 33 reports (5.5%) associated with the injection site or arm, 114 (19%) on localized sites (including 42 on the upper body, 3 on the lower body, 18 on the torso, 11 on the arms and legs, 8 on the legs bilaterally, 10 on the arms bilaterally, and 22 on the face/head), and 8 reports (1%) of fewer than 10 hives scattered over the body. There were 267 reports (44.5%) that did not specify the location of the urticaria. Most reports of urticaria (n=329, 55%) occurred after dose 1, 135 (22%) occurred after dose 2, and 46 (8%) occurred after dose 3. No dose information was provided in 90 reports; 69 of these (77%) were manufacturer reports. The

Table 2. Most Common and Other Selected qHPV Adverse Events Following Immunization in the United States, Reported to VAERS June 1, 2006, Through December 31, 2008

	No. (%)				
AEFI[a]	Serious Adverse Events	Nonserious Events	qHPV Alone[b]	Total, No.	Reporting Rate[c]
Syncope, syncope vasovagal	93 (5)	1803 (95)	1396 (74)	1896	8.2
Local reaction[d]	41 (2)	1700 (98)	1338 (77)	1741	7.5
Dizziness	96 (6)	1476 (94)	1147 (73)	1572	6.8
Nausea	119 (10)	1045 (90)	908 (78)	1164	5.0
Headache	150 (16)	787 (84)	688 (73)	937	4.1
Hypersensitivity reaction[e]	47 (6)	678 (94)	582 (80)	725	3.1
Urticaria	22 (4)	590 (96)	501 (82)	612	2.6
Venous thromboembolic event	39 (69)	17 (31)	55 (98)	56	0.2
Autoimmune disorder	19 (37)	32 (63)	45 (88)	51	0.2
Guillain-Barré syndrome	31 (74)	11 (26)	25 (60)	42	0.2
Anaphylaxis	8 (29)	20 (71)	18 (64)	28	0.1
Death	32 (100)	0	23 (72)	32	0.1
Transverse myelitis	10 (100)	0	10 (100)	10	0.04
Pancreatitis	9 (100)	0	9 (100)	9	0.04
Motor neuron disease	2 (100)	0	2 (100)	2	0.009

Abbreviations: AEFI, adverse event following immunization; qHPV, quadrivalent human papillomavirus recombinant vaccine; VAERS, Vaccine Adverse Event Reporting System.
[a] Using MedDRA terms. More than 1 code may be assigned to a single report.
[b] No other vaccine was coadministered.
[c] Reports per 100 000 doses distributed.
[d] Local injection site reaction MedDRA codes include injection site abscess, injection site abscess sterile, injection site atrophy, injection site cyst, injection site desquamation, injection site hemorrhage, injection site hypersensitivity, injection site inflammation, injection site mass, injection site necrosis, injection site nodule, injection site edema, and injection site pain.
[e] Hypersensitivity reaction MedDRA codes include anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, cross-sensitivity reaction, dermographism, hypersensitivity, urticaria, urticaria thermal, and urticaria vesicular.

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median time interval from immunization to onset of symptoms was 17 days, with a range of 8 to 49 days. The overall RR was 2.6 cases per 100 000 doses distributed.

There were 28 reports coded as anaphylaxis after qHPV (Table 2). Two cases were hearsay reports without any medical information, leaving 26 cases for review. Seventeen of these cases (65%) occurred after dose 1, 4 (15%) occurred after dose 2, 1 case (4%) occurred after dose 3, and the dose number was unknown for 4 cases (15%). Review using the Brighton classification criteria found that 7 (27%) did not meet the criteria for anaphylaxis, 9 (35%) had insufficient information, and 10 (38%) met the Brighton anaphylaxis definition. Only 4 cases were of sufficient concern to be referred to an allergist. Twenty-five cases occurred on the same day as immunization. One case occurred 5 days after immunization; while this case met the Brighton case definition, it was thought unlikely to be vaccine related due to the prolonged time between immunization and onset of symptoms. The overall RR was 0.1 case per 100 000 doses distributed.

Guillain-Barré Syndrome

There were 42 cases of GBS reported to VAERS (Table 2). Twenty-six of the reports were made by the manufacturer with no identifying information to enable clinical review of the cases. After FDA contact of the manufacturer to request information on these cases of interest, additional medical information was obtained on 13 cases (50%). One reporter refused to provide the manufacturer with any identifying information. Six cases were hearsay reports and no further information could be obtained. No further identifying information was provided on 5 cases. Review of the 21 cases with available clinical information showed that 12 cases (57%) met the Brighton case definition, 1 case (5%) initially thought to be an atypical case of GBS was diagnosed as amyotropic lateral sclerosis at autopsy, 2 cases (10%) lacked sufficient detail for complete evaluation, 5 (24%) reported events did not meet the Brighton case definition, and 1 case (5%) occurred prior to vaccination. Medical records are still being collected for the 11 recent cases.

Eleven of 12 confirmed cases were patients aged between 13 and 30 years. Six patients had received qHPV alone; 4 received qHPV and quadrivalent meningococcal conjugate vaccine; 1 received qHPV, quadrivalent meningococcal conjugate vaccine, and hepatitis A vaccine; and 1 received qHPV, quadrivalent meningococcal conjugate vaccine, and varicella vaccine. Onset intervals for the 12 definite cases ranged from 0 to 145 days. Only 8 of the confirmed cases were within the 4- to 42-day window of biological plausibility.[18] The RR of GBS following qHPV was 0.3 confirmed cases per 100 000 person-years. The PRR for GBS after qHPV in 6- to 29-year-olds compared with all other vaccines in 6- to 29-year-olds was 0.4. This PRR did not meet the screening criteria for signal detection.

Transverse Myelitis

There were 10 cases of transverse myelitis reported to VAERS (Table 2). Two cases had insufficient information for adequate clinical review and 1 case was diagnosed as multiple sclerosis. All 7 confirmed transverse myelitis cases were found after qHPV vaccine alone. The age distribution of cases was 13 to 26 years. One case occurred after dose 1, and 6 cases occurred after dose 2. Only 1 case occurred within the theoretical 4- to 42-day window of biological plausibility.[18]

Motor Neuron Disease

There were 3 reports to VAERS of young females who presented with a rapidly progressing neurologic disorder occurring some months after receipt of the qHPV vaccine. One of these reports was a hearsay report (a fifth-hand report) that could not be identified and might represent 1 of the other 2 cases. Autopsy confirmed a diagnosis of amyotropic lateral sclerosis (anterior motor neuron disease) in 1 case. The other young female died in 2009. The autopsy findings on this case are still pending.

Venous Thromboembolic Events

Based on MedDRA search terms of *venous thrombosis*, *thrombosis*, *embolism*, *pulmonary embolism*, *deep vein thrombosis*, *pulmonary thrombosis*, and *embolic stroke*, there were 56 reports of VTEs after qHPV, for an RR of 0.2 case per 100 000 doses. Ten cases were hearsay reports that could not be confirmed or clinically evaluated, 9 reports were related to "clots with menses" and were not VTEs, 5 were manufacturer reports with no identifying information for follow-up, 1 report had insufficient information available for adequate evaluation, and 31 reports had sufficient information for clinical review. There were 5 reports of deep vein thrombosis alone, 7 reports of deep vein thrombosis with pulmonary embolism, 12 reports of pulmonary embolism without deep vein thrombosis, 4 reports of cerebrovascular accidents, 1 report of superior mesenteric vein thrombosis, and 2 reports of superior sagittal venous thrombosis. There were 4 deaths reported among the 19 pulmonary embolism cases (21%).

Thirty of 31 reports (97%) were associated with qHPV immunization alone. The mean age of individuals reported to have VTEs after qHPV immunization was 21 years (median, 20 years; range, 15-39 years). The number of doses preceding the diagnosis of a VTE included 9 cases after dose 1, 11 cases after dose 2, and 10 cases after dose 3; dose number was unknown for 1 case. The mean time between qHPV immunization and diagnosis was 41.5 days (median, 23 days; range, 0-306 days).

Risk factors included estrogen-containing birth control (n=20), family history (n=10), history of smoking (n=2), immobility (n=7), overweight (n=6), increased triglycerides (n=1), history of surgery (n=1), pregnancy (n=2), trauma from surfing (n=1), and hyperviscosity from diabetic ketoacidosis (n=1). Twenty-eight of 31 cases (90%) had a known risk factor for VTEs. Twenty-two of 31 cases (71%) were tested for hypercoagulability; 10 were positive, including 2 cases with factor V Leiden deficiency, 2 cases

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with methylenetetrahydrofolate reductase deficiency, 1 case with methylenetetrahydrofolate reductase deficiency with increased homocysteine levels, 1 case with the prothrombin gene mutation with methylenetetrahydrofolate reductase deficiency, 1 case with a prothrombin mutation and increased homocysteine levels, and 2 cases of antiphospholipid syndrome. All 10 cases with hypercoagulability had a known risk factor for VTEs, including 7 with a history of taking estrogen-containing birth control medications.

The PRR for 6- to 17-year-olds was 4.8 (χ^2=4.16, P=.04). The PRR for 18- to 29-year-olds was 6.7 (χ^2=7.48, P=.006). Both of these age groups met the screening criteria for signal detection.

Pancreatitis

There were 10 reports coded as pancreatitis in VAERS. One case was ultimately diagnosed with multiple ovarian cysts as the cause of the patient's right lower quadrant pain, leaving 9 reports of pancreatitis. All of the cases had risk factors for pancreatitis, including gallstones (n=2), alcohol use (n=1), increased triglycerides (n=1), viral infection (*Coxsackie*) (n=1), estrogen use (n=2), and mild obesity (n=2). All cases were hospitalized, meeting the FDA definition of a serious AEFI. Three cases presented after dose 1, 3 after dose 2, and 3 after dose 3. Two of the individuals who presented after dose 1 had resolution of symptoms but experienced subsequent exacerbations after doses 2 and 3. It was not possible to do any statistical comparisons because of low numbers.

Autoimmune Disorders

There were 51 reports of autoimmune disorders to the VAERS system, including 26 reports of autoimmune disorder (not otherwise specified), 1 report of scleroderma, 1 report of dermatomyositis, 18 reports of systemic lupus erythematosus, 13 reports of rheumatoid arthritis, 1 report of Sjögren syndrome, and 4 reports of mixed connective tissue disease. Fifty-one of these reports (88%) were associated with qHPV vaccine alone.

Pregnancy

There were 236 VAERS reports of qHPV given shortly before or during pregnancy. Twelve of the AEFI reports were coded as serious; 10 required hospitalization due to miscarriage and 2 cases included a life-threatening illness (1 deep vein thrombosis and 1 severe vaginal hemorrhage after emergency dilation and curettage). Two hundred twenty-eight reports (97%) were received from the manufacturer through the Merck Pregnancy Registry.

One hundred forty-three of the reports were coded as miscarriage (spontaneous abortion), including 1 molar pregnancy. There were 75 reports of elective termination of pregnancy following administration of qHPV. None of the reports described receipt of qHPV having influenced the decision to terminate the pregnancy. There were 13 deliveries of normal, healthy infants; 3 ectopic pregnancies; and 2 unknown pregnancy outcomes.

Deaths

There were 32 VAERS reports of death following qHPV vaccination (Table 2). Eight of the reports were second-hand reports that could not be verified. Four were manufacturer reports with no identifying information for confirmation or medical review. Twenty of the reports (62.5%) could be verified through clinical review of medical records and autopsy reports. Of these cases, 14 (70%) were after qHPV alone. The other 6 cases reported qHPV as well as a variety of other vaccines. Nine cases occurred after dose 1, 5 after dose 2, and 6 after dose 3.

Mean age was 18 years (median, 17 years; range, 12-26 years). There was no clustering by age. The mean time from last qHPV immunization to AEFI onset was 39 days (median, 14.5 days; range, 2-288 days). The mean time from last qHPV immunization to death was 47 days (median, 14.5 days; range, 2 to 405 days).

Causes of death included 4 unexplained deaths, 2 cases of diabetic ketoacidosis (1 complicated by pulmonary embolism), 1 case related to prescription drug abuse, 1 case of juvenile amyotropic lateral sclerosis, 1 case of meningoencephalitis (*Neisseria meningitidis* serogroup B), 1 case of influenza B viral sepsis, 3 cases of pulmonary embolism (1 associated with hyperviscosity due to diabetic ketoacidosis), 6 cardiac-related deaths (4 arrhythmias and 2 cases of myocarditis), and 2 cases due to idiopathic seizure disorder.

The PRR for deaths in 6- to 17-year-olds was 1.4 (χ^2=0.42, P=.52). The PRR for deaths in 8- to 29-year-olds was 1.2 (χ^2=0.01, P=.92). Neither of these met the screening criteria for signal detection.

COMMENT

Our review of 12 424 reports of AEFIs following receipt of qHPV after licensure found that most did not meet the FDA definition of serious. The safety profile described by these data for frequent AEs is consistent with prelicensure data, with the exception of syncope and VTEs. This review summarizes passive surveillance data from more than 23 million doses distributed in the United States. Such postlicensure monitoring allows for the potential detection of rare AEFIs as more people are vaccinated. As expected with increased numbers of immunizations in the postlicensure setting, rare AEFIs were observed more often than in the prelicensure review.

Ongoing monitoring will help assess whether the serious reports to VAERS, as well as the few serious AEs identified during prelicensure trials, require further evaluation.[22] The Vaccine Safety Datalink is providing additional surveillance through the use of rapid cycle analyses to monitor for seizures, syncope, anaphylaxis, appendicitis, GBS, and VTEs.[23] Important identified concerns from either VAERS or the Vaccine Safety Datalink can be investigated using well-designed, systematic, hypothesis-driven studies.

Reported deaths with available records, autopsy reports, or death certificates describe causes other than recent vaccination. Two of 3 VTE death

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reports described the use of oral contraceptives, which can increase the risk of VTE 3- to 6-fold.[24] Because the population of young women who frequently use hormonal contraceptives overlaps with those receiving the qHPV vaccine, coincidental occurrences of VTE among qHPV recipients may be anticipated. Nonetheless, close monitoring continues for VTE reports to VAERS following qHPV and other vaccines.

Vasovagal syncope is among the most frequently reported AEFIs following qHPV. When it results in falls, significant traumatic injuries can occur.[25,26] The ACIP and *Red Book* have published guidelines to prevent vasovagal syncope and related injury following vaccination.[27,28] After several newly licensed adolescent vaccines (qHPV; quadrivalent meningococcal conjugate vaccine; and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine) were added to the routine immunization schedule, the number of postvaccination syncope reports to VAERS increased, primarily among females aged 11 to 18 years.[29] This age group also has a higher background rate of syncope than other age groups. The predominance of females could be related to an actual difference between the sexes or could represent reporting bias since the qHPV vaccine is currently licensed for females only. With the increased use of adolescent vaccines, we strongly urge vaccine providers to diligently implement the ACIP recommendations for a routine 15-minute waiting period following vaccination. There have been reports in the literature documenting seizure-like activity during syncope in children.[30,31] Some reports to VAERS of seizures may be anoxic seizures resulting from syncopal episodes.

Reports of VTEs after qHPV immunization should be interpreted with caution due to the multiple limitations of a passive reporting system and the potential effect of widespread media coverage stimulating reporting. These cases occurred over a wide time interval after immunization, and 90% reported a known risk factor for VTEs. It is difficult to establish a potential window of biological plausibility since the time frame between risk factor exposure and clot formation is unknown. We did not detect any signal for VTEs through data mining or in the Vaccine Safety Datalink. Continued monitoring will be done for cases in VAERS, the Vaccine Safety Datalink, and potential future studies.

Our review of definite and possible GBS reports revealed a lower RR (0.3/100 000 estimated person-years based on dose distribution) than the background incidence rate of GBS in 9- to 26-year-old females (1.57/100 000 person-years). We did not detect any signal for GBS through data mining or in the Vaccine Safety Datalink, although the extent of underreporting to VAERS is not known.[20]

Because there are no adequate and well-controlled studies in pregnant women, and animal reproduction studies are not always predictive of human response, qHPV is not recommended for use in pregnant women.[1] Exposures to qHPV during pregnancy have been identified in VAERS. As agreed with the FDA at the time of licensure, the vaccine manufacturer established a voluntary pregnancy registry to monitor outcomes among women vaccinated with qHPV during the month prior to conception or during pregnancy.[1] This pregnancy registry is more complete than VAERS reporting and includes continued follow-up of cases.

Although VAERS shares inherent limitations of all passive surveillance systems, it is national in scope and can provide important signals that may require further attention.[8] However, VAERS data need to be interpreted with caution, because not all reported events are systematically validated, and many may have only coincidentally followed vaccination. In addition, data limitations include underreporting, inconsistency in the quality and completeness of reported data, stimulated reporting due to extensive news coverage, and reporting biases.[7] The VAERS reporting rate for qHPV is triple the rate for all other vaccines combined, perhaps reflecting greater public attention to HPV than the usual increased reporting following licensure of a new product ("Weber effect").[32,33] AEFI reporting rates also need cautious interpretation, because vaccine distribution data do not allow calculation of age-specific reporting rates and do not provide the numbers of doses actually administered.

A further limitation of VAERS reports after qHPV is that a large proportion (68%) come from the manufacturer and most of these reports (89%) do not include sufficient identifying information to allow medical review of the individual cases. For example, when additional clinical information was available for review, approximately one-half of the cases of GBS and transverse myelitis were not confirmed.

Postlicensure safety surveillance of qHPV supplements data from the prelicensure randomized clinical trials. Ongoing VAERS monitoring also complements 2 large ongoing postlicensure observational safety studies: the CDC-sponsored Vaccine Safety Datalink "rapid cycle analysis" and a phase IV study agreed on by the manufacturer and the FDA at the time of vaccine licensure.[1,34] The latter study will provide data on the safety of simultaneous use of qHPV with other recommended vaccines, as well as autoimmune and serious AEFIs reported after qHPV vaccination. The pregnancy registry will continue for at least 5 years.

CONCLUSION

Vaccination with qHPV has the potential to decrease the global morbidity and mortality of HPV-associated diseases, including cervical cancer. After hepatitis B vaccine, which can prevent liver cancer, qHPV is only the second vaccine licensed with an indication to prevent cancer. The postlicensure safety profile presented here is broadly consistent with safety data from prelicensure trials. Because VAERS data must be interpreted cautiously and cannot generally be used to infer causal asso-

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ciations between vaccines and AEFIs, postlicensure monitoring will continue, and identified signals may be evaluated using epidemiologic observational studies.

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Acquisition of data: Leidel, Vellozzi, Izurieta, Miller.
Analysis and interpretation of data: Slade, Leidel, Vellozzi, Woo, Hua, Sutherland, Izurieta, Ball, Braun, Markowitz, Iskander.
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Administrative, technical, or material support: Slade, Leidel, Ball, Braun, Markowitz.
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